

PATENT COOPERATION TREATY

PCT

NOTIFICATION OF ELECTION

(PCT Rule 61.2)

From the INTERNATIONAL BUREAU

To:

Assistant Commissioner for Patents
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in its capacity as elected Office

Date of mailing (day/month/year)

14 December 1999 (14.12.99)

International application No.

PCT/US99/10187

Applicant's or agent's file reference

5716-01-CA

International filing date (day/month/year)

10 May 1999 (10.05.99)

Priority date (day/month/year)

26 May 1998 (26.05.98)

Applicant

DOBRUSIN, Ellen, Myra et al

1. The designated Office is hereby notified of its election made:



in the demand filed with the International Preliminary Examining Authority on:

25 November 1999 (25.11.99)



in a notice effecting later election filed with the International Bureau on:

2. The election ☒ was

was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

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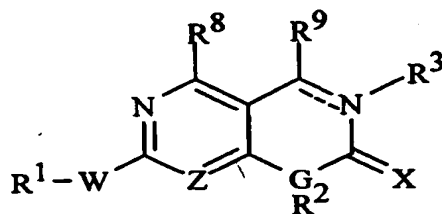
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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁶ : C07D 487/04, 471/04, A61K 31/505 // (C07D 487/04, 239:00, 239:00) (C07D 471/04, 239:00, 221:00)		A2	(11) International Publication Number: WO 99/61444 (43) International Publication Date: 2 December 1999 (02.12.99)
(21) International Application Number: PCT/US99/10187 (22) International Filing Date: 10 May 1999 (10.05.99) (30) Priority Data: 60/086,708 26 May 1998 (26.05.98) US 60/126,158 25 March 1999 (25.03.99) US (71) Applicant (for all designated States except US): WARNER-LAMBERT COMPANY [US/US]; 201 Tabor Road, Morris Plains, NJ 07950 (US). (72) Inventors; and (75) Inventors/Applicants (for US only): DOBRUSIN, Ellen, Myra [US/US]; 2205 Winchell, Ann Arbor, MI 48104 (US). HAMBY, James, Marino [US/US]; 4390 Chad Court, Ann Arbor, MI 48103 (US). KRAMER, James, Bernard [US/US]; 7128 Grenlock Drive, Sylvania, OH 43560 (US). SCHROEDER, Mel, Conrad [US/US]; 7858 Ridgeway Court, Dexter, MI 48130 (US). SHOWALTER, Howard, Daniel, Hollis [US/US]; 3578 Lamplighter Drive, Ann Arbor, MI 48103 (US). TOOGOOD, Peter [GB/US]; 2281 Sun Valley Drive, Ann Arbor, MI 48108 (US). TRUMPP-KALLMEYER, Susanne, A. [DE/SE]; Gundefjaellsgatan 411, S-431 51 Moelndal (SE).		(74) Agents: RYAN, M., Andrea; Warner-Lambert Company, 201 Tabor Road, Morris Plains, NJ 07950 (US) et al. (81) Designated States: AE, AL, AU, BA, BB, BG, BR, CA, CN, CU, CZ, EE, GD, GE, HR, HU, ID, IL, IS, JP, KP, KR, LC, LK, LR, LT, LV, MG, MK, MN, MX, NO, NZ, PL, RO, SG, SI, SK, SL, TR, TT, UA, US, UZ, VN, YU, ZA, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG). Published Without international search report and to be republished upon receipt of that report.	

(54) Title: BICYCLIC PYRIMIDINES AND BICYCLIC 3,4-DIHYDROPYRIMIDINES AS INHIBITORS OF CELLULAR PROLIFERATION



(I)

(57) Abstract

This invention provides bicyclic heterocycles that are useful for treating cell proliferative disorders, such as cancer and restenosis, as well as angiogenesis and atherosclerosis. We have now discovered a group of bicyclic compounds that are potent inhibitors of cyclin-dependent kinases (cdks), growth factor-mediated kinases, and non-receptor kinases. The compounds are readily synthesized and can be administered by a variety of routes, including orally, and have sufficient bioavailability for clinical use. This invention provides compounds of Formula (I), where Z is N or CH; G is N or CH; W is NH, S, SO, or SO₂, R¹ includes phenyl and substituted phenyl, R² includes alkyl and cycloalkyl, R³ includes alkyl and hydrogen, R⁸ and R⁹ include hydrogen and alkyl, and the pharmaceutically acceptable salts thereof. This invention also provides pharmaceutical formulations comprising a compound of Formula (I) together with a pharmaceutically acceptable carrier, diluent, or excipient therefor.

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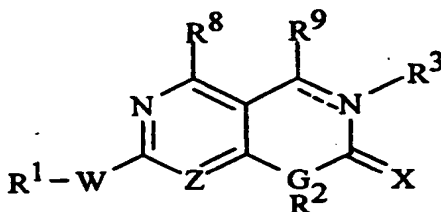
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(21) International Application Number: PCT/US99/10187		(43) International Publication Date: 2 December 1999 (02.12.99)	
(22) International Filing Date: 10 May 1999 (10.05.99)		(74) Agents: RYAN, M., Andrea; Warner-Lambert Company, 201 Tabor Road, Morris Plains, NJ 07950 (US) et al.	
(30) Priority Data: 60/086,708 26 May 1998 (26.05.98) US 60/126,158 25 March 1999 (25.03.99) US		(81) Designated States: AE, AL, AU, BA, BB, BG, BR, CA, CN, CU, CZ, EE, GD, GE, HR, HU, ID, IL, IS, JP, KP, KR, LC, LK, LR, LT, LV, MG, MK, MN, MX, NO, NZ, PL, RO, SG, SI, SK, SL, TR, TT, UA, US, UZ, VN, YU, ZA, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).	
(71) Applicant (for all designated States except US): WARNER-LAMBERT COMPANY [US/US]; 201 Tabor Road, Morris Plains, NJ 07950 (US).		Published With international search report. Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.	
(72) Inventors; and (75) Inventors/Applicants (for US only): DOBRUSIN, Ellen, Myra [US/US]; 2205 Winchell, Ann Arbor, MI 48104 (US). HAMBY, James, Marino [US/US]; 4390 Chad Court, Ann Arbor, MI 48103 (US). KRAMER, James, Bernard [US/US]; 7128 Grenlock Drive, Sylvania, OH 43560 (US). SCHROEDER, Mel, Conrad [US/US]; 7858 Ridgeway Court, Dexter, MI 48130 (US). SHOWALTER, Howard, Daniel, Hollis [US/US]; 3578 Lamplighter Drive, Ann Arbor, MI 48103 (US). TOOGOOD, Peter [GB/US]; 2281 Sun Valley Drive, Ann Arbor, MI 48108 (US). TRUMPP-KALLMEYER, Susanne, A. [DE/SE]; Gundefjaellsgatan 411, S-431 51 Moelndal (SE).		(88) Date of publication of the international search report: 3 February 2000 (03.02.00)	

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INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 99/10187

A. CLASSIFICATION OF SUBJECT MATTER

IPC 6 C07D487/04 C07D471/04 A61K31/505 //(C07D487/04, 239:00, 239:00), (C07D471/04, 239:00, 221:00)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 96 34867 A (WARNER-LAMBERT CO.) 7 November 1996 (1996-11-07) claims 1,46 ---	1,43
Y	US 5 654 307 A (A. J. BRIDGES ET AL.) 5 August 1997 (1997-08-05) column 1, line 15 - line 19 column 4, line 65 - column 5, line 14 column 7, line 34 - line 63 column 9, line 21 - line 48 claim 1 ---	1,43
Y	WO 95 19774 A (WARNER-LAMBERT CO.) 27 July 1995 (1995-07-27) abstract; claims 71,74 ---	1,43
	-/--	



Further documents are listed in the continuation of box C.



Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

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Date of the actual completion of the international search

9 December 1999

Date of filing of the international search report

16/12/1999

Name and mailing address of the ISA

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NL - 2280 HV Rijswijk
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INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 99/10187

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 97 38983 A (WARNER-LAMBERT CO.) 23 October 1997 (1997-10-23) abstract; claims 1,36 ----	1,43
Y	G. W. REWCASTLE ET AL.: JOURNAL OF MEDICINAL CHEMISTRY, vol. 39, 1996, pages 1823-35, XP002046257 page 1823, abstract; page 1826, table 1 ----	1
Y	G. W. REWCASTLE TE AL.: JOURNAL OF MEDICINAL CHEMISTRY, vol. 38, 1995, pages 3482-7, XP000673491 page 3482, abstract; page 3484, table 1 ----	1
A	EP 0 278 686 A (THE WELLCOME FOUNDATION LTD.) 17 August 1988 (1988-08-17) claims 1,7,8 ----	1,43
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A	WO 96 15128 A (WARNER-LAMBERT CO.) 23 May 1996 (1996-05-23) claims 1,46 ----	1,43
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A,P	WO 98 33798 A (WARNER LAMBERT CO.) 6 August 1998 (1998-08-06) claims 1,26 ----	1,43
A,P	WO 99 09030 A (WARNER-LAMBERT CO.) 25 February 1999 (1999-02-25) abstract; claims 1,65 ----	1,43
A,P	WO 99 06378 A (WARNER-LAMBERT CO.) 11 February 1999 (1999-02-11) abstract; claims 1,27 -----	1,43

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 99/ 10187

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 25-41
because they relate to subject matter not required to be searched by this Authority, namely:
Although claims 25-41 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition (Rule 39.1 (iv) PCT - Method for treatment of the human or animal body by therapy).
2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

information on patent family members

International Application No

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		US 4661490 A	28-04-1987
		ZA 8003539 A	27-01-1982
		US 4959474 A	25-09-1990
WO 9833798 A	06-08-1998	AU 6648098 A	25-08-1998
		HR 980060 A	30-06-1999
WO 9909030 A	25-02-1999	AU 8828998 A	08-03-1999
WO 9906378 A	11-02-1999	AU 8760798 A	22-02-1999

PATENT COOPERATION TREATY

PCT

REC'D 14 JUN 2000

WIPO

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference 5716-01-CA		FOR FURTHER ACTION See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)	
International application No. PCT/US99/10187	International filing date (day/month/year) 10/05/1999	Priority date (day/month/year) 26/05/1998	
International Patent Classification (IPC) or national classification and IPC C07D487/04			
Applicant WARNER-LAMBERT COMPANY et al.			

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.



2. This REPORT consists of a total of 6 sheets, including this cover sheet.

☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:

- I ☒ Basis of the report
- II ☐ Priority
- III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- IV ☐ Lack of unity of invention
- V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- VI ☒ Certain documents cited
- VII ☐ Certain defects in the international application
- VIII ☒ Certain observations on the international application

Date of submission of the demand 25/11/1999	Date of completion of this report 09.06.2000
Name and mailing address of the international preliminary examining authority:  European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer Ladenburger, C Telephone No. +49 89 2399 8276 

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT**

International application No. PCT/US99/10187

I. Basis of the report

1. This report has been drawn on the basis of (*substitute sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments.*):

Description, pages:

1-105 as originally filed

Claims, No.:

1-43 as originally filed

2. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
☐ the claims, Nos.:
☐ the drawings, sheets:

3. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

4. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

- ☐ the entire international application.
☒ claims Nos. 25-41 as to IA.

because:

- ☒ the said international application, or the said claims Nos. 25-41 relate to the following subject matter which does not require an international preliminary examination (*specify*):

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/US99/10187

see separate sheet

- ☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):
- ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.
- ☐ no international search report has been established for the said claims Nos. .

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	2-13,15-24,42
	No:	Claims	1,14,25-41,43
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-43
Industrial applicability (IA)	Yes:	Claims	1-24,42,43
	No:	Claims	

2. Citations and explanations

see separate sheet

VI. Certain documents cited

1. Certain published documents (Rule 70.10)

and / or

2. Non-written disclosures (Rule 70.9)

see separate sheet

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT**

International application No. PCT/US99/10187

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

see separate sheet

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT - SEPARATE SHEET**

International application No. PCT/US99/10187

III. Non-establishment of opinion

Claims 25-41 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(i) PCT).

V.2 Reasoned statement; Citations and explanations

1. Reference is made to the following documents cited in the ISR:

D1= WO-A-95/19774

D4= WO-A-96/34867

D2= US-A-5 654 307

D5= WO-A-96/15128

D3= WO-A-97/38983

2. Compounds of formula I according to claim 1 and their use as tyrosine kinases and cellular proliferation inhibitors have already been disclosed in the prior art document D1 (and in the corresponding US Patent D2), see e.g. claims 74-77, Formula II. The subject-matter of claims 1, 14, 25-41 and 43 is therefore not novel. It is reminded that not only the specific working examples but also any reproducible technical teaching described in the prior art documents, i.e. the whole overlapping range with D1, must be disclaimed in order to establish novelty.
3. Even if novelty could formally be established, no inventive step could be seen in the claimed subject-matter, since the use of this type of compounds as tyrosine kinases and cellular proliferation inhibitors was already known in the state of the art (see 2. above and D3-D5).

Moreover, it is reminded that the breadth of the claims should be such that it represents a reasonable generalisation over the examples provided, and such that every compound falling within its scope actually provides a solution to the problem underlying the invention.

In the present case, having regard to the limited variety of the compounds effectively prepared and tested, it is questionable whether the scope of claims 1-43 is reasonable and justified. Further, it is considered that terms such as "substituted",

"heteroaryl", "heterocyclyl", "alkyl", "aldehyde" or "oxime ether" used throughout the claims without further indication, e.g. of the number and nature of the substituents or heteroatoms, of the size of the rings or number of carbon atoms, are vague and indefinite, and can lead to speculative compounds which do not exhibit the alleged properties. Thus the Applicant should ensure that principal claim 1 covers only compounds which actually solve the given problem of providing novel tyrosine kinases and cellular proliferation inhibitors.

4. For the assessment of claims 25-41 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

VI. Certain documents cited

The P-documents cited in the ISR D6= WO-A-98/33798, D7= WO-A-99/09030 and D8= WO-A-99/06378 do not disclose novelty destroying matter, but would also be pertinent for the assessment of inventive step if the priority date of the present application were not valid (same type of compounds, same use).

VIII. Certain observations

1. Ar is not defined in claim 1.
2. Claims 6,9,11,13,16,19,22,24,42 comprise all the features of claim 1 and are therefore not appropriately formulated as claims dependent on the latter.
3. Claims 25,26,30,34 could be shortened by means of a reference to claim 1 for the compounds of Formula I.
Z,G,W,X are not defined in claims 25 and 26.

Rose Armstrong

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To:

MANSMANN, Ivo / TESCH, Rudolf
Warner-Lambert Company
Legal Division
c/o Gödecke AG, Patents
Mooswaldallee 1
D-79090 Freiburg
ALLEMAGNE

Patentwesen

Eing.: 13. Juni 2000

NOTIFICATION OF TRANSMITTAL OF
THE INTERNATIONAL PRELIMINARY
EXAMINATION REPORT
(PCT Rule 71.1)

Date of mailing
(day/month/year)

09.06.2000

Applicant's or agent's file reference

5716-01-CA

IMPORTANT NOTIFICATION

International application No.
PCT/US99/10187

International filing date (day/month/year)
10/05/1999

Priority date (day/month/year)
26/05/1998

Applicant

WARNER-LAMBERT COMPANY et al.

1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary examination report and its annexes, if any, established on the international application.
2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.
3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.

4. REMINDER

The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices) (Article 39(1)) (see also the reminder sent by the International Bureau with Form PCT/IB/301).

Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary examination report. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide.

Name and mailing address of the IPEA/



European Patent Office
D-80298 Munich
Tel. +49 89 2399 - 0 Tx: 523656 epmu d
Fax: +49 89 2399 - 4465

Authorized officer

Brell, S

Tel. +49 89 2399-7271



PTO/PCT 07 SEP 2000

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PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT



(PCT Article 36 and Rule 70)

Applicant's or agent's file reference 5716-01-CA	FOR FURTHER ACTION See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)	
International application No. PCT/US99/10187	International filing date (day/month/year) 10/05/1999	Priority date (day/month/year) 26/05/1998
International Patent Classification (IPC) or national classification and IPC C07D487/04		
Applicant WARNER-LAMBERT COMPANY et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 6 sheets, including this cover sheet.
 - ☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:
 - I ☒ Basis of the report
 - II ☐ Priority
 - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
 - IV ☐ Lack of unity of invention
 - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
 - VI ☒ Certain documents cited
 - VII ☐ Certain defects in the international application
 - VIII ☒ Certain observations on the international application

Date of submission of the demand 25/11/1999	Date of completion of this report 09.06.2000
Name and mailing address of the international preliminary examining authority:  European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer Ladenburger, C Telephone No. +49 89 2399 8276 

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT**

International application No. PCT/US99/10187

I. Basis of the report

1. This report has been drawn on the basis of (*substitute sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments.*):

Description, pages:

1-105 as originally filed

Claims, No.:

1-43 as originally filed

2. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
☐ the claims, Nos.:
☐ the drawings, sheets:

3. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

4. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

- ☐ the entire international application.
☒ claims Nos. 25-41 as to IA.

because:

- ☒ the said international application, or the said claims Nos. 25-41 relate to the following subject matter which does not require an international preliminary examination (*specify*):

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT**

International application No. PCT/US99/10187

see separate sheet

- ☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):
- ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.
- ☐ no international search report has been established for the said claims Nos. .

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes: Claims 2-13,15-24,42
	No: Claims 1,14,25-41,43
Inventive step (IS)	Yes: Claims
	No: Claims 1-43
Industrial applicability (IA)	Yes: Claims 1-24,42,43
	No: Claims

2. Citations and explanations

see separate sheet

VI. Certain documents cited

1. Certain published documents (Rule 70.10)

and / or

2. Non-written disclosures (Rule 70.9)

see separate sheet

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT**

International application No. PCT/US99/10187

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

see separate sheet

III. Non-establishment of opinion

Claims 25-41 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(i) PCT).

V.2 Reasoned statement; Citations and explanations

1. Reference is made to the following documents cited in the ISR:

D1= WO-A-95/19774

D4= WO-A-96/34867

D2= US-A-5 654 307

D5= WO-A-96/15128

D3= WO-A-97/38983

2. Compounds of formula I according to claim 1 and their use as tyrosine kinases and cellular proliferation inhibitors have already been disclosed in the prior art document D1 (and in the corresponding US Patent D2), see e.g. claims 74-77, Formula II. The subject-matter of claims 1, 14, 25-41 and 43 is therefore not novel. It is reminded that not only the specific working examples but also any reproducible technical teaching described in the prior art documents, i.e. the whole overlapping range with D1, must be disclaimed in order to establish novelty.
3. Even if novelty could formally be established, no inventive step could be seen in the claimed subject-matter, since the use of this type of compounds as tyrosine kinases and cellular proliferation inhibitors was already known in the state of the art (see 2. above and D3-D5).

Moreover, it is reminded that the breadth of the claims should be such that it represents a reasonable generalisation over the examples provided, and such that every compound falling within its scope actually provides a solution to the problem underlying the invention.

In the present case, having regard to the limited variety of the compounds effectively prepared and tested, it is questionable whether the scope of claims 1-43 is reasonable and justified. Further, it is considered that terms such as "substituted",

"heteroaryl", "heterocyclyl", "alkyl", "aldehyde" or "oxime ether" used throughout the claims without further indication, e.g. of the number and nature of the substituents or heteroatoms, of the size of the rings or number of carbon atoms, are vague and indefinite, and can lead to speculative compounds which do not exhibit the alleged properties. Thus the Applicant should ensure that principal claim 1 covers only compounds which actually solve the given problem of providing novel tyrosine kinases and cellular proliferation inhibitors.

4. For the assessment of claims 25-41 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

VI. Certain documents cited

The P-documents cited in the ISR D6= WO-A-98/33798, D7= WO-A-99/09030 and D8= WO-A-99/06378 do not disclose novelty destroying matter, but would also be pertinent for the assessment of inventive step if the priority date of the present application were not valid (same type of compounds, same use).

VIII. Certain observations

1. Ar is not defined in claim 1.
2. Claims 6,9,11,13,16,19,22,24,42 comprise all the features of claim 1 and are therefore not appropriately formulated as claims dependent on the latter.
3. Claims 25,26,30,34 could be shortened by means of a reference to claim 1 for the compounds of Formula I.
Z,G,W,X are not defined in claims 25 and 26.

NOTED

DEC 21 1999

PATENT COOPERATION TREATY

R. ARMSTRONG

From the INTERNATIONAL SEARCHING AUTHORITY

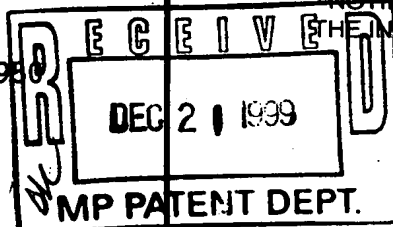
PCT/ISA/220 (July 1993) 07 SEP 2000

PCT

To:

WARNER-LAMBERT COMPANY
201 Tabor Road
Morris Plains, New Jersey 07980
UNITED STATES OF AMERICA

07980



NOTIFICATION OF TRANSMITTAL OF
THE INTERNATIONAL SEARCH REPORT
OR THE DECLARATION

(PCT Rule 44.1)

Date of mailing
(day/month/year)

16/12/1999

Applicant's or agent's file reference

5716-01-CA

FOR FURTHER ACTION

See paragraphs 1 and 4 below

International application No.

PCT/US 99/ 10187

International filing date
(day/month/year)

10/05/1999

Applicant

WARNER-LAMBERT COMPANY et al.

1. ☒ The applicant is hereby notified that the International Search Report has been established and is transmitted herewith.

Filing of amendments and statement under Article 19:

The applicant is entitled, if he so wishes, to amend the claims of the International Application (see Rule 46):

When? The time limit for filing such amendments is normally 2 months from the date of transmittal of the International Search Report; however, for more details, see the notes on the accompanying sheet.

Where? Directly to the International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland
Facsimile No.: (41-22) 740.14.35

For more detailed instructions, see the notes on the accompanying sheet.

2. ☐ The applicant is hereby notified that no International Search Report will be established and that the declaration under Article 17(2)(a) to that effect is transmitted herewith.

3. ☐ With regard to the protest against payment of (an) additional fee(s) under Rule 40.2, the applicant is notified that:

☐ the protest together with the decision thereon has been transmitted to the International Bureau together with the applicant's request to forward the texts of both the protest and the decision thereon to the designated Offices.

☐ no decision has been made yet on the protest; the applicant will be notified as soon as a decision is made.

4. **Further action(s):** The applicant is reminded of the following:

Shortly after 18 months from the priority date, the international application will be published by the International Bureau. If the applicant wishes to avoid or postpone publication, a notice of withdrawal of the international application, or of the priority claim, must reach the International Bureau as provided in Rules 90bis.1 and 90bis.3, respectively, before the completion of the technical preparations for international publication.

Within 19 months from the priority date, a demand for international preliminary examination must be filed if the applicant wishes to postpone the entry into the national phase until 30 months from the priority date (in some Offices even later).

Within 20 months from the priority date, the applicant must perform the prescribed acts for entry into the national phase before all designated Offices which have not been elected in the demand or in a later election within 19 months from the priority date or could not be elected because they are not bound by Chapter II.

Name and mailing address of the International Searching Authority



European Patent Office, P.B. 5818 Patentlaan 2
NL-2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax (+31-70) 340 2040

Authorized officer

Chantal Meyer

NOTES TO FORM PCT/ISA/220

These Notes are intended to give the basic instructions concerning the filing of amendments under article 19. The Notes are based on the requirements of the Patent Cooperation Treaty, the Regulations and the Administrative Instructions under that Treaty. In case of discrepancy between these Notes and those requirements, the latter are applicable. For more detailed information, see also the PCT Applicant's Guide, a publication of WIPO.

In these Notes, "Article", "Rule", and "Section" refer to the provisions of the PCT, the PCT Regulations and the PCT Administrative Instructions respectively.

INSTRUCTIONS CONCERNING AMENDMENTS UNDER ARTICLE 19

The applicant has, after having received the international search report, one opportunity to amend the claims of the international application. It should however be emphasized that, since all parts of the international application (claims, description and drawings) may be amended during the international preliminary examination procedure, there is usually no need to file amendments of the claims under Article 19 except where, e.g. the applicant wants the latter to be published for the purposes of provisional protection or has another reason for amending the claims before international publication. Furthermore, it should be emphasized that provisional protection is available in some States only.

What parts of the International application may be amended?

Under Article 19, only the claims may be amended.

During the international phase, the claims may also be amended (or further amended) under Article 34 before the International Preliminary Examining Authority. The description and drawings may only be amended under Article 34 before the International Examining Authority.

Upon entry into the national phase, all parts of the international application may be amended under Article 28 or, where applicable, Article 41.

When?

Within 2 months from the date of transmittal of the international search report or 16 months from the priority date, whichever time limit expires later. It should be noted, however, that the amendments will be considered as having been received on time if they are received by the International Bureau after the expiration of the applicable time limit but before the completion of the technical preparations for international publication (Rule 46.1).

Where not to file the amendments?

The amendments may only be filed with the International Bureau and not with the receiving Office or the International Searching Authority (Rule 46.2).

Where a demand for international preliminary examination has been/is filed, see below.

How?

Either by cancelling one or more entire claims, by adding one or more new claims or by amending the text of one or more of the claims as filed.

A replacement sheet must be submitted for each sheet of the claims which, on account of an amendment or amendments, differs from the sheet originally filed.

All the claims appearing on a replacement sheet must be numbered in Arabic numerals. Where a claim is cancelled, no renumbering of the other claims is required. In all cases where claims are renumbered, they must be renumbered consecutively (Administrative Instructions, Section 205(b)).

The amendments must be made in the language in which the international application is to be published.

What documents must/may accompany the amendments?

Letter (Section 205(b)):

The amendments must be submitted with a letter.

The letter will not be published with the international application and the amended claims. It should not be confused with the "Statement under Article 19(1)" (see below, under "Statement under Article 19(1)").

The letter must be in English or French, at the choice of the applicant. However, if the language of the international application is English, the letter must be in English; if the language of the international application is French, the letter must be in French.

NOTES TO FORM PCT/ISA/220 (continued)

The letter must indicate the differences between the claims as filed and the claims as amended. It must, in particular, indicate, in connection with each claim appearing in the international application (it being understood that identical indications concerning several claims may be grouped), whether

- (i) the claim is unchanged;
- (ii) the claim is cancelled;
- (iii) the claim is new;
- (iv) the claim replaces one or more claims as filed;
- (v) the claim is the result of the division of a claim as filed.

The following examples illustrate the manner in which amendments must be explained in the accompanying letter:

1. [Where originally there were 48 claims and after amendment of some claims there are 51]:
"Claims 1 to 29, 31, 32, 34, 35, 37 to 48 replaced by amended claims bearing the same numbers; claims 30, 33 and 36 unchanged; new claims 49 to 51 added."
2. [Where originally there were 15 claims and after amendment of all claims there are 11]:
"Claims 1 to 15 replaced by amended claims 1 to 11."
3. [Where originally there were 14 claims and the amendments consist in cancelling some claims and in adding new claims]:
"Claims 1 to 6 and 14 unchanged; claims 7 to 13 cancelled; new claims 15, 16 and 17 added." or
"Claims 7 to 13 cancelled; new claims 15, 16 and 17 added; all other claims unchanged."
4. [Where various kinds of amendments are made]:
"Claims 1-10 unchanged; claims 11 to 13, 18 and 19 cancelled; claims 14, 15 and 16 replaced by amended claim 14; claim 17 subdivided into amended claims 15, 16 and 17; new claims 20 and 21 added."

"Statement under article 19(1)" (Rule 46.4)

The amendments may be accompanied by a statement explaining the amendments and indicating any impact that such amendments might have on the description and the drawings (which cannot be amended under Article 19(1)).

The statement will be published with the international application and the amended claims.

It must be in the language in which the international application is to be published.

It must be brief, not exceeding 500 words if in English or if translated into English.

It should not be confused with and does not replace the letter indicating the differences between the claims as filed and as amended. It must be filed on a separate sheet and must be identified as such by a heading, preferably by using the words "Statement under Article 19(1)."

It may not contain any disparaging comments on the international search report or the relevance of citations contained in that report. Reference to citations, relevant to a given claim, contained in the international search report may be made only in connection with an amendment of that claim.

Consequence if a demand for international preliminary examination has already been filed

If, at the time of filing any amendments under Article 19, a demand for international preliminary examination has already been submitted, the applicant must preferably, at the same time of filing the amendments with the International Bureau, also file a copy of such amendments with the International Preliminary Examining Authority (see Rule 62.2(a), first sentence).

Consequence with regard to translation of the international application for entry into the national phase

The applicant's attention is drawn to the fact that, where upon entry into the national phase, a translation of the claims as amended under Article 19 may have to be furnished to the designated/elected Offices, instead of, or in addition to, the translation of the claims as filed.

For further details on the requirements of each designated/elected Office, see Volume II of the PCT Applicant's Guide.

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference 5716-01-CA	FOR FURTHER ACTION see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.	
International application No. PCT/US 99/ 10187	International filing date (day/month/year) 10/05/1999	(Earliest) Priority Date (day/month/year) 26/05/1998
Applicant WARNER-LAMBERT COMPANY et al.		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 4 sheets.



It is also accompanied by a copy of each prior art document cited in this report.

1. Basis of the report

- a. With regard to the **language**, the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.



the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

- b. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international search was carried out on the basis of the sequence listing:



contained in the international application in written form.



filed together with the international application in computer readable form.



furnished subsequently to this Authority in written form.



furnished subsequently to this Authority in computer readable form.



the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.



the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

2. ☒ **Certain claims were found unsearchable** (See Box I).

3. ☐ **Unity of invention is lacking** (see Box II).

4. With regard to the **title**,

the text is approved as submitted by the applicant.



the text has been established by this Authority to read as follows:

5. With regard to the **abstract**,

the text is approved as submitted by the applicant.



the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the **drawings** to be published with the abstract is Figure No.

as suggested by the applicant.



because the applicant failed to suggest a figure



because this figure better characterizes the invention.



None of the figures.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 99/10187

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 25-41
because they relate to subject matter not required to be searched by this Authority, namely:
Although claims 25-41 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition (Rule 39.1 (iv) PCT - Method for treatment of the human or animal body by therapy).
2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 99/10187

A. CLASSIFICATION OF SUBJECT MATTER

IPC 6 C07D487/04 C07D471/04 A61K31/505 //(C07D487/04,239:00,
239:00),(C07D471/04,239:00,221:00)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 96 34867 A (WARNER-LAMBERT CO.) 7 November 1996 (1996-11-07) claims 1,46	1,43
Y	US 5 654 307 A (A. J. BRIDGES ET AL.) 5 August 1997 (1997-08-05) column 1, line 15 - line 19 column 4, line 65 - column 5, line 14 column 7, line 34 - line 63 column 9, line 21 - line 48 claim 1	1,43
Y	WO 95 19774 A (WARNER-LAMBERT CO.) 27 July 1995 (1995-07-27) abstract; claims 71,74	1,43
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☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search

9 December 1999

Date of mailing of the international search report

16/12/1999

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (+31-70) 340-3016

Authorized officer

Hass, C

INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 99/10187

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 97 38983 A (WARNER-LAMBERT CO.) 23 October 1997 (1997-10-23) abstract; claims 1,36 ----	1,43
Y	G. W. REWCASTLE ET AL.: JOURNAL OF MEDICINAL CHEMISTRY, vol. 39, 1996, pages 1823-35, XP002046257 page 1823, abstract; page 1826, table 1 ----	1
Y	G. W. REWCASTLE TE AL.: JOURNAL OF MEDICINAL CHEMISTRY, vol. 38, 1995, pages 3482-7, XP000673491 page 3482, abstract; page 3484, table 1 ----	1
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A,P	WO 98 33798 A (WARNER LAMBERT CO.) 6 August 1998 (1998-08-06) claims 1,26 ----	1,43
A,P	WO 99 09030 A (WARNER-LAMBERT CO.) 25 February 1999 (1999-02-25) abstract; claims 1,65 ----	1,43
A,P	WO 99 06378 A (WARNER-LAMBERT CO.) 11 February 1999 (1999-02-11) abstract; claims 1,27 -----	1,43

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